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(57) Abstract

A process for preparing felbamate and a key intermediate, 2-phenyl-1, 3-propanediol (PPD) is disclosed. PPD can be prepared by contacting (i) the enolate salt of formyl phenyl acid ester (VIII), (ii) an E-enol (X), a Z-enol (XII) or formylphenylacetic acid ester (XIV), (iii) a tropate (XIII), (iv) a tropate borate (XV) or mixtures thereof, with an acid and a borohydride reducing agent in an amount effective to give PPD. In another embodiment, PPD can also be prepared by cleaving, optionally in the presence of an acid, (v) a borate ester (XVI), (vi) a boric acid ester (XVII) or mixtures thereof. Felbamate can be prepared from wet or dry PPD by reaction with either (a) a cyanate and a strong acid in a non-halogenated solvent; or (b) chlorosulfonyl isocyanate in a suitable solvent.

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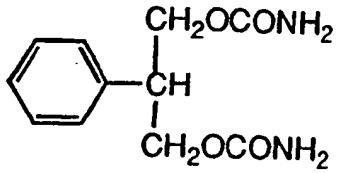
PROCESS FOR PREPARING FELBAMATE, 2-PHENYL-1,3-PROPANEDIOL AND INTERMEDIATES

BACKGROUND

Felbamate, known as 2-phenyl-1,3-propanediol dicarbamate, shown below



(I)

is a potent antiepileptic compound useful for treating various types of epilepsy. Felbamate is described in U.S. Patent 2,884,444 and 4,978,680. The compound 2-phenyl-1,3-propanediol (PPD) is a valuable intermediate for preparing felbamate, but there are problems in commercial operation due to safety considerations during manufacturing, high expenses associated with its preparation, environmental and waste disposal problems, and generally low yields achieved by known processes.

U.S. Patents 4,982,016 (1991), 5,072,056 (1992) and 5,091,595 (1992) describe various processes for preparing PPD from diethyl phenylmalonate. However, these known processes suffer the disadvantage of requiring costly and extremely flammable agents for reducing diethyl phenylmalonate to PPD, such as borane dimethyl sulfide, aluminum hydrides such as lithium aluminum hydride and diisobutyl aluminum hydride. The high cost and hazardous nature of such reducing agents renders such processes unsatisfactory for commercial use in a tonnage production plant. PPD of formula (XVIII) can be converted to 2-phenyl-1,3-propanediol dicarbamate (felbamate) by methods, such as those described in U.S. Patent 4,868,327, 5,091,595 and B.J. Ludwig et al., J. Med. Chem., Vol. 12(3), 1969, pp. 462-472 using environmentally undesirable halogenated solvents such as chloroform and halogenated acids such as trifluoroacetic acid and trichloroacetic acid.

Efforts to resolve the above problems associated with diethyl phenylmalonate reduction led to the development of a multi-step process for producing PPD, based on benzaldehyde, as taught in U.S. Patent 4,868,327. This reference teaches a process utilizing formation of benzaldehyde oxime and peracetic acid oxidation to phenyl nitromethane,

followed by reaction with formaldehyde and catalytic reduction of the resulting nitro phenyl propanediol to PPD. This process avoids the limitations and hazards associated with the reducing agents discussed above, but introduces several new hazards and costs. For instance, peracetic acid and nitroalkane intermediates pose potential runaway reaction and even explosion risks, formaldehyde is listed as a cancer suspect agent and catalytic hydrogenation is well known to pose fire hazards. In addition, the yields of PPD taught in U.S. Patent 4,868,327 are low, while the chemical handling and disposal problems associated with the several process steps introduce environmental concerns.

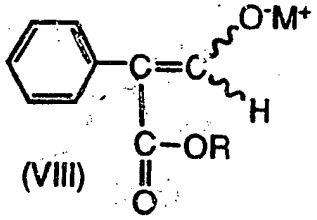
U.S.S.R. (SU) Patent Application 322988, February 25, 1976 discloses a method for preparing tropic acid by the reduction of alkyl esters of formylphenylacetic acid with borohydrides of alkali metals in which only the aldehyde moiety (i.e. -CHO) is reduced, followed by hydrolysis. This reference fails to teach a process whereby both the aldehyde and the ester moiety are reduced. It would be desirable to provide a process for preparing felbamate and its intermediate, PPD, safely, in as few or even fewer steps than other processes previously taught, in good yields with little formation of undesirable by-products, with less waste to dispose of or recycle, such as halogenated solvents or acids.

SUMMARY OF THE INVENTION

The present invention is directed toward a process for preparing 2-phenyl-1,3-propanediol (PPD), comprising:

reacting a compound which is:

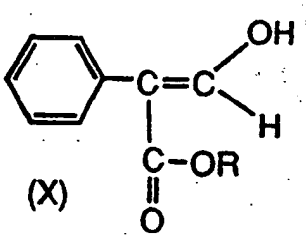
i) the enolate salt of formylphenylacetic acid ester (VIII)



(VIII)

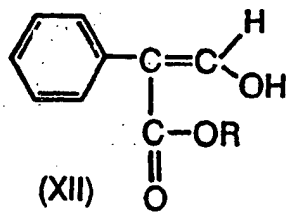
;

ii) an E-enol (X), a Z-enol (XII) or formylphenylacetic acid ester (XIV)



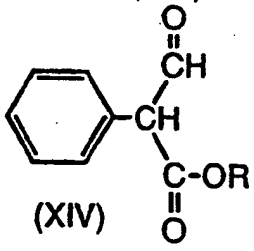
(X)

,



(XII)

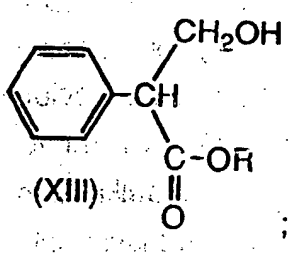
or



(XIV)

;

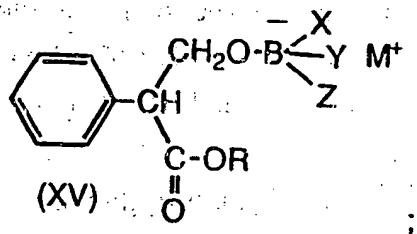
iii) a tropate (XIII)



(XIII)

;

iv) a tropate borate (XV)



(XV)

; or

vii) or a mixture of i-iv) above, wherein

M is a cation, such as a metal of Groups I, II or III in the periodic table, titanium or ammonium;

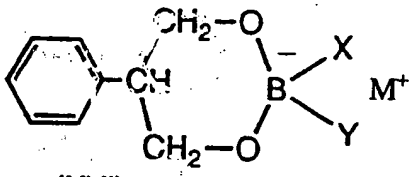
R is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, arylalkyl, substituted arylalkyl, heterocyclic, heterocyclic alkyl, aryl or substituted aryl;

X, Y and Z independently represent H, -OH, $-O^-M^+$, $-O-R^2$ or $-OCOR^2$ where M is as defined hereinabove, R^2 is C-1 to C-6 alkyl;

with an acid and a borohydride reducing agent in an amount effective to give PPD.

In another embodiment the present invention is directed toward a process for preparing 2-phenyl-1,3-propanediol (PPD-XVIII), comprising cleaving, optionally in the presence of an acid, a compound which is:

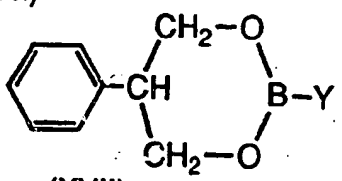
v) a borate ester (XVI)



(XVI)

;

vi) a boric acid ester (XVII)



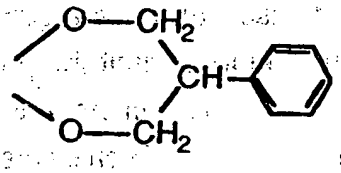
(XVII)

; or

vii) a mixture of v-vi);

wherein M is a cation, such as a metal of Groups I, II or III in the periodic table, titanium or ammonium;

X and Y independently represent H, -OH, $-O^-M^+$, $-O-R^2$ or $-OCOR^2$ where M is as defined hereinabove, R^2 is C-1 to C-6 alkyl, and with the proviso that in the borate ester (XVI), X and Y together can represent a diester of the formula:



to give PPD.

In this embodiment, borate ester (XVI), boric acid ester (XVII) or a mixture thereof can be cleaved by distillation or by extraction of the boron-moiety from the borate ester (XVI), boric acid ester (XVII) or mixture thereof. In procedures where distillation is employed, the boron-moiety can be cleaved by transesterification and distillation of volatile borates formed therefrom. In procedure where extraction is employed, the boron-moiety can be cleaved by extracting the borate ester (XVI), boric acid ester (XVII) or mixture thereof with water and a suitable organic solvent.

In another embodiment, the present process further comprises the step of converting the 2-phenyl-1,3-propanediol (PPD) from any of the above intermediates, routes or processes to 2-phenyl-1,3-propanediol dicarbamate (felbamate).

In another embodiment, the enolate salt of formyl phenyl acetic acid ester (VIII) is prepared by contacting an ester of phenyl acetic acid (II) with an ester of formic acid (IV) in the presence of a base of the formula:

MA (VI)

wherein M is a cation, such as a metal of Groups I, II or III in the periodic table, titanium or ammonium; and wherein A is an anion which enables MA to function as a base, to give the enolate salt of formylphenylacetic acid ester (VIII). In this embodiment, preferably the ester of phenylacetic acid (II) is methyl phenyl acetate, the base is sodium methoxide and the ester of formic acid (IV) is methyl formate.

In another embodiment, the present invention is directed toward novel boron-containing intermediates such as tropate borate (XV), borate ester (XVI) and a boric acid ester (XVII).

In yet another embodiment, the present invention is directed toward a process for preparing felbamate, comprising contacting 2-phenyl-1,3-propanediol with either

a) a cyanate and dry, gaseous hydrogen chloride or bromide in a non-halogenated solvent which can provide felbamate in a yield of about 70% or greater in the reaction mixture; or

b) chlorosulfonyl isocyanate in a suitable solvent.

In another embodiment the present invention is directed toward a process for preparing felbamate which comprises converting the hydroxy groups of PPD to $-OCONH_2$ characterized in that the PPD used as a starting material is produced using any of the procedures described above.

One advantage of the present invention is that it provides a process for preparing felbamate and PPD in higher yields and purity than other known processes. Another advantage of the present invention is that it provides a process for preparing felbamate and PPD more safely than other processes previously taught. Another advantage of the present invention is that it provides a process for preparing felbamate and PPD at lower cost and thus more economically, utilizing conventional process equipment for implementation on a large tonnage scale. And still yet another advantage of the present process is that it can employ enolate salts of formylphenyl acetic acid esters as a starting material. These enolate salts can be easily separated or isolated from the reaction mixture in which they are prepared, and can be stored for subsequent reaction. The present invention has the advantage of providing a process for preparing felbamate and PPD having reduced chemical handling and disposal problems, thus minimizing impact upon the environment. And still yet another advantage of the present process is that the conversion of the starting materials and intermediates thereof to PPD can be accomplished at high process throughput in a continuous process sequence suitable for the automated production of both felbamate and PPD. Such high process throughput or automated production can significantly reduce manufacturing costs.

DETAILED DESCRIPTION OF THE INVENTION

When utilized herein the terms listed below, unless indicated otherwise, are defined as follows:

alkyl - represents a straight chain saturated hydrocarbon moiety having from 1 to 10, preferably from 1 to 6 carbon atoms or a branched hydrocarbon moiety of 3 to 10 carbon atoms, preferably from 3 to 6, such as for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, decyl and the like; the term "substituted alkyl" refers to an alkyl moiety in which one or more of the hydrogen atoms can be substituted with halo, hydroxyl, alkyl, aryl or cycloalkyl;

alkoxy - represents an alkyl moiety covalently bonded to an adjacent structure through an oxygen atom, such as for example, methoxy, ethoxy, propoxy, butoxy, hexoxy and the like.

cycloalkyl - represents a saturated carbocyclic ring containing from 3 to 7 carbon atoms, such as for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like; the term "substituted cycloalkyl" refers to an cycloalkyl moiety in which one or more of the hydrogen atoms can be substituted with halo, hydroxyl, alkyl, aryl or cycloalkyl;

alkenyl - represents a straight chain hydrocarbon chain hydrocarbon moiety of two to 10 carbon atoms or a branched hydrocarbon moiety of three to 10 carbon atoms having at least one carbon-to-carbon double bond such as ethenyl , 1-propenyl, 1-butenyl, 2-butenyl, isobutenyl, 1-pentenyl, 2-methyl-1-butenyl, 1-hexenyl and the like;

aryl - represents a carbocyclic moiety containing at least one benzenoid-type ring, with the aryl moiety having from 6 to 14 carbon atoms,with all available substitutable carbon atoms of the aryl moiety being intended as possible points of attachment, for example phenyl, naphthyl, indenyl, indanyl and the like, and wherein said carbocyclic moiety can be optionally substituted with one to three moieties independently selected from the following: halo, alkyl, trifluoromethyl, phenyl, hydroxy, alkoxy, phenoxy, amino, monoalkylamino or dialkylamino; the term "substituted aryl" refers to an aryl moiety substituted with one to three substituents independently selected from aryl, alkyl, alkoxy, halo, trihalomethyl, cyano, nitro, $-CONH_2$, hydroxy, protected hydroxy, hydroxyalkyl, protected hydroxyalkyl, mercapto or carboxy and salts or esters thereof;

arylalkyl or substituted arylalkyl - refers to a an aryl or substituted aryl moiety bonded to an adjacent structural element through an alkyl moiety, such as for example phenylmethyl, 2-chlorophenylethyl, 2-methoxyphenylethyl and the like;

chlorinated hydrocarbons - refers to a hydrocarbon in which one or more of the hydrogen atoms has been replaced by fluorine, chlorine, bromine or iodine. Representative chlorinated hydrocarbons include chloroform, carbon tetrachloride, chlorobenzene and trifluoromethane.

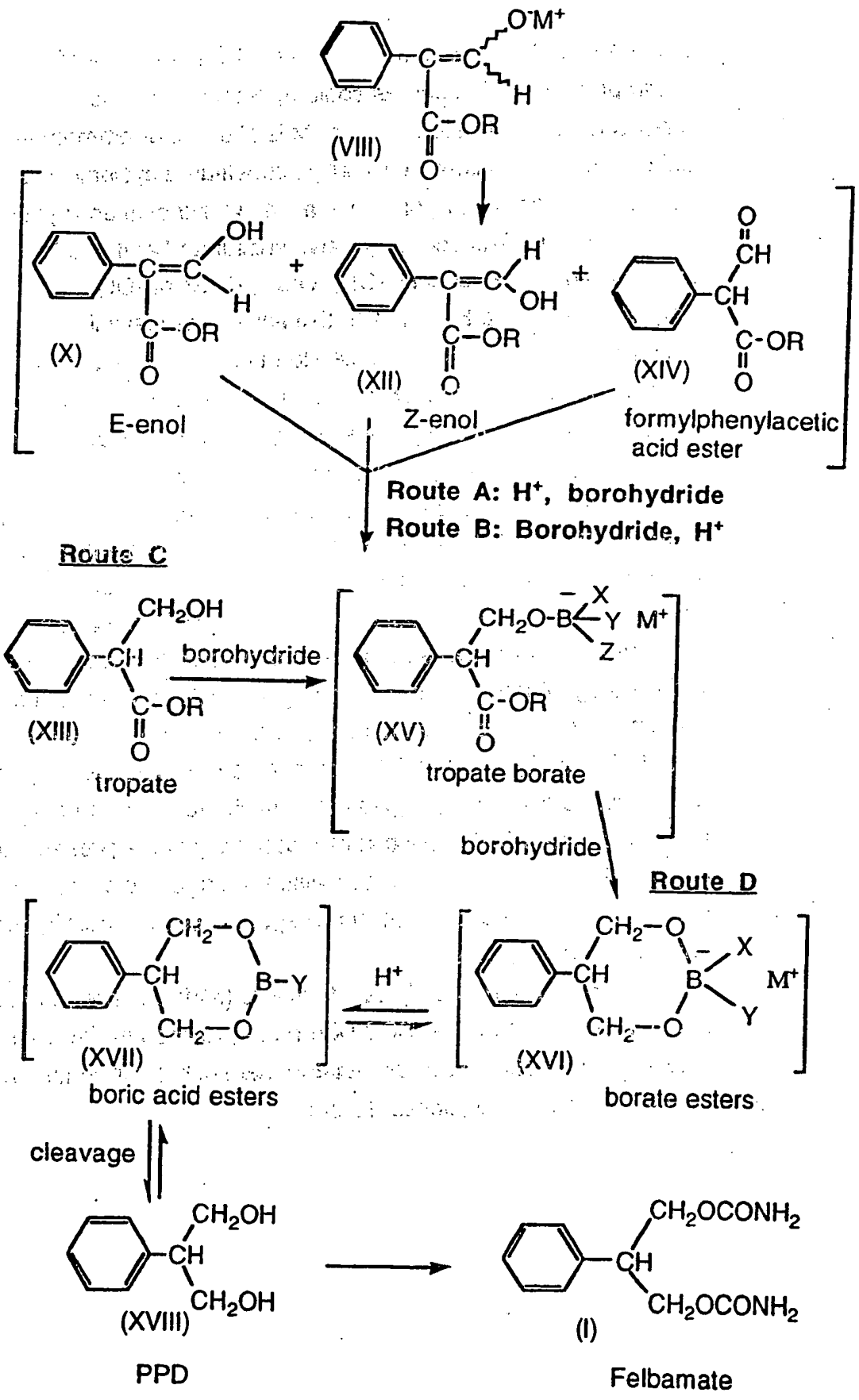
halo - represents fluoro, chloro, bromo or iodo;

heterocyclic - represents a cyclic group having at least one O, S and/or N interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably from 2 to 6 carbon atoms, for example 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 1, 2-, 4- or 5-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 3- or 5-[1,2,4-thiadazolyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl and the like;

heterocyclic alkyl - represents a heterocyclic moiety bonded to an adjacent structural element through an alkyl moiety.

boron-moiety - refers to the moiety of borate ester (XVI), boric acid ester (XVII) or a mixture thereof containing a boron atom, whose cleavage or removal from the borate ester (XVI), boric acid ester (XVII) or a mixture thereof gives PPD .

The present process and embodiments thereof are illustrated as follows.

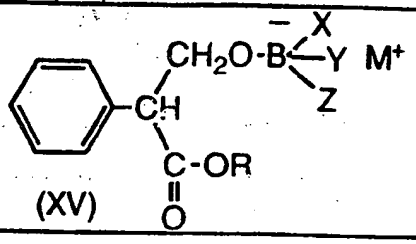

(VIII)
(X)
E-enol
(XII)
Z-enol
(XIV)
formylphenylacetic acid ester
Route A: H+, borohydride
Route B: Borohydride, H+
Route C
(XIII)
tropate
borohydride
(XV)
tropate borate
borohydride
Route D
(XVII)
boric acid esters
H+
(XVI)
borate esters
cleavage
(XVIII)
PPD
(I)
Felbamate

In the above illustration, M is a cation, such as a metal of Groups I, II or III in the periodic table such as sodium, potassium, lithium, calcium, magnesium, zinc or aluminum, or M is titanium or ammonium; R is alkyl, substituted alkyl, alkoxy, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, arylalkyl, substituted arylalkyl, heterocyclic, heterocyclic alkyl, aryl, substituted aryl and X, Y and Z independently represent H, -OH, $-O^-M^+$, $-O-R^2$ or $-OCOR^2$ wherein M is as defined above, and R^2 is C-1 to C-6 alkyl. The wavy line "~~~~" indicates that the substituents can form either the cis or trans configurations about the double bond. The brackets ([ ]) indicate intermediates which are generally not, but could be isolated from the reaction mixture during the preparation of PPD.

The above process can be performed via several routes. In one route (ie. Route A) the enolate salt of formylphenylacetic acid ester (VIII) is contacted first with an acid and then with the borohydride reducing agent to give PPD. In another route (ie. Route B), the enolate salt of formylphenylacetic acid ester (VIII) is contacted first with the borohydride reducing agent and then with acid to give PPD. In Routes A and B, preferably, the enolate salt is methyl 2-formyl-2-phenyl acetate sodium salt. In Route C, tropate (XIII) is contacted with borohydride, optionally in the presence of an acid, to give PPD. In Route D, borate esters (XVI) and boric acid esters (XVII) are cleaved, optionally in the presence of an acid, to give PPD. In the above routes, also preferred is that the acid is sulfuric acid or acetic acid and the reducing agent is sodium borohydride or potassium borohydride.

Tropate borates (XV), borate esters (XVI) and boric acid esters (XVII) useful for preparing PPD (XVIII) are provided in Tables 1, 2 and 3, respectively. It should be appreciated that such compounds can also form the more complex polyborate esters.

Table 1. Tropate borates (XV)



(XV)

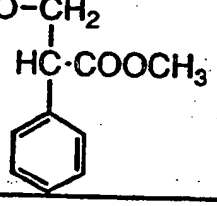
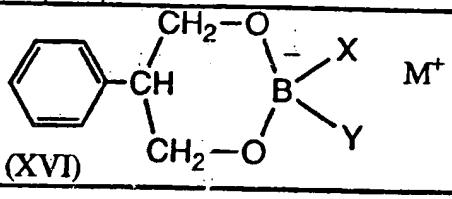
	X	Y	Z	R	M
1.	-H	-H	-H	$-CH_3$	Na
2.	-H	-H	-H	$-CH_3$	K
3.	-H	-H	-H	$-CH_3$	Li
4.	-OH	-H	-H	$-CH_3$	Na
5.	$-OCH_2CH_3$	-H	-H	$-CH_3$	Na
6.	$-OCH_2CH_2CH_3$	-H	-H	$-CH_3$	Na
7.	$-OCH(CH_3)_2$	-H	-H	$-CH_3$	Na
8.	$-OCH_2CH_2CH_2CH_3$	-H	-H	$-CH_3$	Na
9.	$-OCOCH_3$	-H	-H	$-CH_3$	Na
10.		-H	-H	$-CH_3$	Na

Table 2. Borate Esters (XVI)



(XVI)

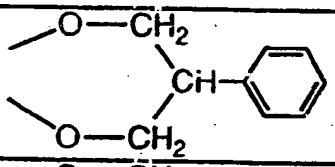
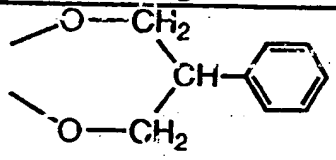
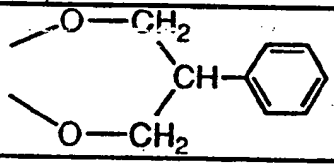
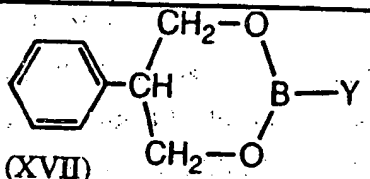
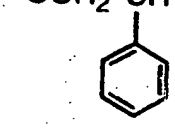
	X	Y	M
1.	-OH	-OH	Na
	monoester; ^{1}H NMR (DMSO): 2.8 (q, 6.5 Hz, 1), 3.6 (d of d of d's, 10.5, 6.5 and 5.3 Hz, 1), 3.7 (d of d of d's, 10.5, 6.5 and 5.3 Hz, 1), 4.5 (t, 5.3 Hz, 2), 7.1-7.3 (m, 5). ^{11}B NMR (DMSO): -18.2		
2.	-OH	-OH	K
3.	-OH	-OH	Li
4.			Na
5.			K
	diester; ^{1}H NMR (DMSO): 2.75 (t of t's, 10 and 5 Hz, 2), 3.6 (broad mutiplet, 4), 3.75 (t, 10 Hz, 2), 3.80 (t, 10 Hz, 2), 7.1-7.3 (m, 10). ^{11}B NMR (DMSO): -18.6		
6.			Li
7.	-OH	$-OCOCH_3$	Na
8.	-OH	$-OCOCH_3$	K
9.	-OH	$-O(CH_2)_3CH_3$	Na
10.	-OH	$-O(CH_2)_3CH_3$	K
11.	$-OCOCH_3$	$-OCOCH_3$	Na
12.	$-OCOCH_3$	$-OCOCH_3$	K
13.	-OH	$-OCH_2CH_2CH_3$	Na
14.	-OH	$-OCH(CH_3)_2$	Na

Table 3. Boric acid esters (XVII)



(XVII)

	Y	
1.	-OH	^{1}H NMR (DMSO): 3.17 (t of t's, 10.3 and 4.5 Hz, 1), 3.99 (d of d's, 10.3 and 4.5 Hz, 2), 4.07 (t, 10.3 Hz, 2), 7.1-7.4 (m, 5). ^{11}B NMR (DMSO): -1.5
2.	O^-Na^+	
3.	O^-K^+	
4.	O^-Li^+	
5.	$-OCH_3$	
6.	$-OCH_2CH_3$	
7.	$-O(CH_2)_2CH_3$	
8.	$-O(CH)(CH_3)_2$	
9.	$-O(CH_2)_3CH_3$	
10.	$-OCOCH_3$	
11.		

PPD can be prepared by contacting the enolate salt of formyl phenyl acetic acid ester (VIII) with an acid and a borohydride reducing agent in an amount effective to reduce both the aldehyde and the ester moiety. The reactants can be mixed in different orders of addition. In one procedure (ie. Route A), enolate salt (VIII) is contacted with a suitable acid to a form a product which can exist in an equilibrium of compounds (X), (XII) or (XIV), which can be isolated where desired. These compounds can be reduced with a borohydride reducing agent to tropate borate (XV), borate esters (XVI) and boric acid esters (XVII), with subsequent cleavage of borate esters (XVI) and boric acid esters (XVII) to the desired PPD (XVIII). In another procedure (ie. Route B), enolate salt (VIII) can be admixed with a borohydride reducing agent prior to addition of the acid. In this procedure, addition of acid causes the in-situ formation of an

Borohydrides which can be employed in the present process include sodium, potassium, lithium, calcium, zinc and magnesium borohydrides, preferably sodium or potassium, and modified borohydrides prepared by partial reaction of a borohydride with a protic solvent. The borohydride reducing agent can be employed in amounts effective to reduce both the aldehyde and the ester moiety of either enolate salt (VIII), E-enol (X), Z-enol (XII) or formyl phenylacetic acid ester (XIV). Such amounts can range from about equimolar to excess borohydride per mole of enolate salt (VIII), preferably from about 1.1 to about two moles borohydride, preferably from about 1.3 to about 1.7. The term "excess" means an amount of borohydride in excess of the theoretical amount needed to reduce both the aldehyde and the ester moiety of either enolate salt (VIII) or aldehyde enol (X).

The process can be carried out in a solvent compatible with the borohydride reducing agent. Such solvents include protic solvents such as water, C-1 to C-10 alcohols including methanol, ethanol, propanol, isopropanol, butanol and the like. Aprotic solvents such as tetrahydrofuran, toluene, ethers including methyl tertiary butyl ether and diethylether or esters of C-1 to C-5 carboxylic acids including formic, acetic and propionic. Mixtures of any of the above solvents can be employed. The amount of solvent should be sufficient to provide a mixable slurry of the reactants.

The reaction can be carried out at temperatures ranging from about -40°C to the boiling point of the solvent employed, preferably from about -20° to about 40°C, more preferably from about -15°C to about 30°C. Also preferred is that the reactants are contacted at ambient pressures, although pressures greater than ambient can be employed.

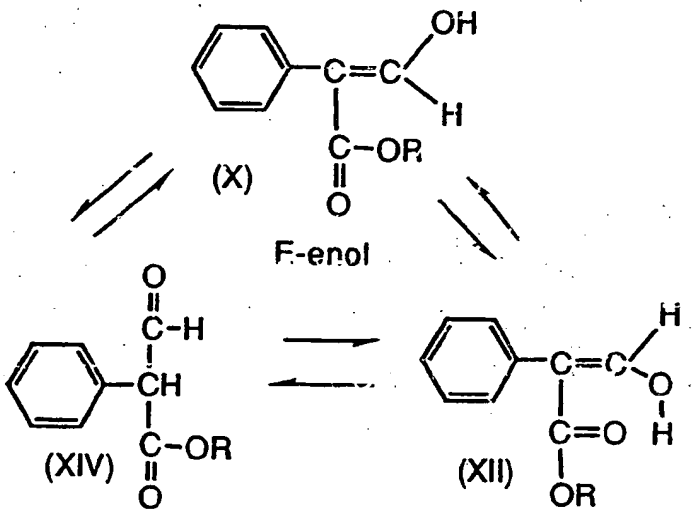
The reactants can be contacted for a time sufficient to allow the desired completion of the reaction, such as from one to 24 hours or more, preferably from about 2 to 8 hours.

Recovery of PPD and other intermediates from the reaction mixture can be made using conventional recovery procedures, such as by extraction, crystallization, filtration and/or removal of any solvents present.

PPD can be converted to felbamate by transesterification with an appropriate ester carbamate. PPD can also be converted to felbamate by reacting PPD with phosgene to form a bis chloroformate, or by reacting

equilibrium of compounds (X), (XII) or (XIV) and the addition of borohydride forms tropate borate (XV), borate ester (XVI) and boric acid ester (XVII), with eventual conversion to the desired PPD (XVIII). Alternatively, the enolate salt, acid and borohydride reducing agent can be combined together at about the same time, ie. simultaneously, in order to prepare PPD. In any of these procedures, PPD can be converted to felbamate using any known procedure, such as urethane exchange or via our new procedures using chlorosulfonyl isocyanate or cyanate and hydrogen chloride.

It will be appreciated that depending upon the solvent, E-enol (X) can exist in various tautomeric forms (XII) and (XIV) before eventual conversion to PPD:



The choice of solvent can influence greatly the equilibrium. For example, in dimethylsulfoxide (DMSO), compound (XII) predominates. In chloroform, all three compounds are present.

Acids which can be employed in the present process include any suitable mineral, organic acid or mixtures thereof. Suitable mineral acids include sulfuric, hydrochloric, phosphoric, boric and the like. Suitable organic acids include acetic, citric, formic, maleic, tartaric, methanesulfonic and the like. The acid can be neat or admixed with an organic solvent or water. The acids can be employed in amounts effective to protonate enolate salt (VIII). Such amounts can range from about equimolar to excess per mole of enolate salt (VIII), preferably from about equimolar to about two moles of acid.

PPD with a phenyl chloro formate (Ph-OCOCl) to form a bis carbonate, followed by treatment with ammonia.

PPD can be advantageously, and most economically, converted to felbamate via our new process which uses a cyanate and a strong acid in a non-halogenated solvent. The reaction mixture can be maintained at a temperature ranging from about -20°C to the boiling point of the reaction mixture, preferably from about -15°C to about 50°C, more preferably about -10°C to about 40°C, most preferably about -5°C to about 35°C. Suitable cyanates include cyanates and isocyanates of the formula:

$$T^{n+}(NCO)_n^- \quad (XXII)$$

wherein T is hydrogen or a cation, such as a metal of Groups I, II or III in the periodic table, titanium or ammonium and n (the valency) can be an integer from 1 to 10, preferably n is 1 to 4. Representative cyanates include sodium cyanate (NaOCN), potassium cyanate (KOCN), ammonium cyanate (NH_4OCN), magnesium cyanate ($Mg(OCN)_2$), aluminum cyanate ($Al(OCN)_3$) and titanium cyanate ($Ti(OCN)_4$). The amount of cyanate can range from about 2 to about 10 moles of cyanate per mole of PPD, preferably from about 2 to about 4 moles, more preferably from about 2 to about 2.5 moles of cyanate. Suitable strong acids include inorganic acids and organic acids. Strong inorganic acids are hydrogen chloride, hydrogen bromide, sulfuric acid, nitric acid, perchloric acid and mixtures thereof. Strong organic acids include methanesulfonic acid and arylsulfonic acids of the formula $ArSO_3H$, wherein Ar is aryl such as phenyl or substituted phenyl, including tolyl, nitrophenyl, xylyl, and the like. The amount of the strong acid can range from about equimolar to about 2 moles of acid per mole of cyanate, preferably from about 1.05 to about 1.3 moles of acid. Preferably the acid contains less than 50% water, more preferably less than 5%. Such non-halogenated solvents include but are not limited to N-dialkylacetamide(C_{1-6}alkyl); acetonitrile; dimethyl sufoxide (DMSO); ethers such as ethylene glycol dimethyl ether (DME, a monoglyme), bis-(2-methoxyethyl)ether (a diglyme), ethylene glycol diethyl ether and diethoxyethane (DEE). The amount of solvent can range from that effective to solubilize the PPD reactant to slightly or greatly excessive amounts and provide felbamate in a yield of about 70% or greater. The yield of felbamate in the reaction mixture can be measured by HPLC or by any other suitable means. The table below demonstrates the pronounced

effect of the solvent upon yield of felbamate under comparable ratios of reactants.

Solvent	Felbamate Yield (%)
chloroform ($CHCl_3$)	45
DME	94
acetonitrile (CH_3CN)	97
N,N-dimethyl acetamide [$CH_3CON(CH_3)_2$]	87
acetone	81

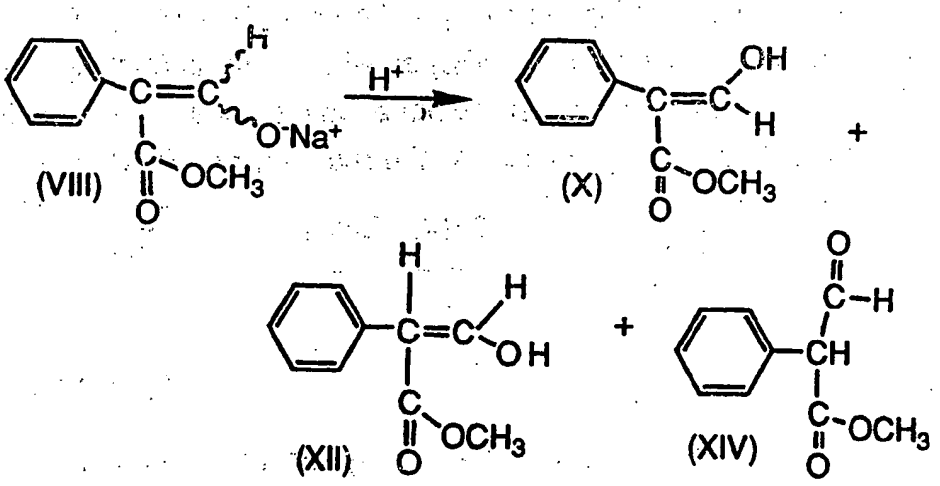
PPD can also be converted to felbamate with our new procedure using a blocked or masked isocyanate, ie. R^3NCO where R^3 is a readily removable protecting group, selected from a silyl group, e.g.

$(CH_3)_3Si$-, $(CH_3)_2Si<$, $CH_3Si\lessdot$, $Si\lessdot$

or an acyl or sulphonyl isocyanate, including chlorosulphonyl isocyanate. Advantageously, felbamate can be converted from PPD which is still wet or moist with solvents, without the need to further process and dry the PPD. This allows for the automated manufacturing of felbamate, with significant cost savings.

The following examples illustrate the present invention in a manner of which it can be practiced, but, as such, should not be construed as limiting the overall scope of the same.

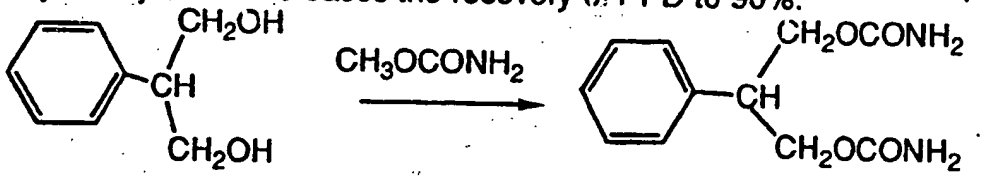
Example 1. Preparation of PPD and felbamate via Route A.



i) The wet cake of methyl 2-formyl-2-phenyl acetate sodium salt (VIII) from the Preparative Example, below, is added to 300 mL of an aqueous 10% v/v sulfuric acid (0.66 equivalents acid) maintained at a temperature of 5-10°C. The mixture is stirred and extracted with two 150 mL washings of ethyl acetate. The combined organic extracts are washed with water and saturated brine, dried over sodium sulfate and filtered. Any remaining solvents are removed by gently warming the organic extracts to a temperature less than 50°C to give methyl 2-formyl-2-phenyl acetate (XIV), an oil which in solution, exists in equilibrium with E-enol (X) and Z-enol (XII).

$$(X) + (XII) + (XIV) \xrightarrow{NaBH_4} PPD$$

ii) methyl 2-formyl -2-phenyl acetate (XIV, 26 g, 0.146 mole) from step i) is dissolved in 30 mL ethanol and added dropwise to a suspension of sodium borohydride (8.3 g, 0.22 mole) in 260 mL ethanol maintained at 15-30°C by external cooling. After the reaction mixture is heated to 50-55°C for about 2 hours, sulfuric acid (200 mL of 3% v/v aqueous) is added dropwise at a temperature of less than 30°C. Following addition of sulfuric acid, the reaction mixture is heated at 50-55° for 30 minutes and vacuum distilled to remove ethanol at a temperature of less than 60°C to give an in-solution yield of PPD of greater than 90%, based upon the enolate salt starting material. The residual product is taken up in 200 mL of ethyl acetate, washed with 100 mL water, 100 mL saturated sodium bicarbonate and 100 mL saturated brine, dried over sodium sulfate and the solvent removed under vacuum. Recrystallization of the residue in 25 mL toluene at 60°C, cooling to ambient temperature and then to 10°C, followed by filtering, washing and drying gives 14.3 g (64% yield) of 2-phenylpropane-1,3-diol (PPD) as white crystals (melting point 54-56°C). Continuous extraction of the aqueous mother liquors with ethyl acetate or methyl t-butyl ether increases the recovery of PPD to 90%.



PPD-(XVIII) Felbamate

iii) To a reaction flask is charged 2-phenyl-1,3-propanediol (PPD-XVIII, 152.2 g, one mole) and 760 mL of toluene. The reaction mixture is

refluxed via Dean-Stark tube to remove any water present. After heat is removed and the temperature of the reaction mixture falls below 65°C, methyl carbamate (160 g, 2.13 moles) and aluminum isopropoxide (15.2 g, 10% weight basis) are charged to the reaction flask. The mixture is heated to reflux (ca. 108°C), ensuring the distillation temperature at the top of the fractionation column does not exceed 65°C. After 6 hours the toluene is stripped off and the reaction mixture is heated under vacuum for 30 minutes. Water (2 L, 13 volumes) is charged to the residue and the mixture is heated to 90-95°C. Concentrated hydrochloric acid (11 mL, 0.07 volumes) is charged to the flask, the addition bottle is rinsed with water (15 ml, 0.1 volumes) and the reaction mixture is agitated at 95°C for 30 minutes. Water (500 mL, 3.3 volumes) is stripped off and the product is allowed to crystallize at ambient temperatures. Cooling the batch to 0°C for 2 hours, filtering and washing with water (one volume) and drying the product at a temperature between 30-60°C gives crude felbamate, (87-89% yield). The product can be further purified by charging crude felbamate (100 g) to a reaction flask, adding methanol (1.2 L, 12 volumes) and heating the product to reflux to effect solution. The hot solution is filtered and some of the methanol is stripped off to give a final volume of about 650 mL. The batch is cooled to ambient temperatures, cooled to 0-5°C for about 2 hours, the product is filtered, washed with methanol (100 mL, one volume) and dried between 30-60°C to give purified felbamate, (85% yield).

Example 2. Preparation of PPD via Route B.

To a 3 liter 3-neck flask equipped with an overhead stirrer, thermometer and Y-tube holding an addition funnel and condenser with nitrogen inlet is charged 1000 mL isopropanol. Sodium borohydride (37.9 g, 1.0 mol) is added and cooled to 10°C. With good agitation, methyl α-formyl phenyl acetate sodium enolate (100 g crude, 80 g active enolate, 0.400 mol active) is charged to the suspension, followed by a slow, dropwise addition of glacial acetic acid (60 mL, 1.04 mol) over 1 hour maintaining a temperature below 30°C. The ice bath is removed after complete addition of glacial acetic acid and the reaction mixture is stirred at room temperature until the sodium enolate has reacted, as determined by high performance liquid chromatography (HPLC). The reaction mixture is warmed to 45°C until all the methyl tropate intermediate has reacted.

The reaction mixture is cooled to 10°C and water (250 mL) is slowly added. Caution is advised, since quenching excess sodium borohydride is exothermic and generated hydrogen gas may foam. The pH is adjusted to 13 with 50% sodium hydroxide (40 mL) and isopropanol is atmospherically distilled at 81°C. After distillation is complete, the slurry is cooled to 40°C and adjusted to pH to 4 with 6N sulfuric acid (290 mL). The yield of PPD in solution, as determined by HPLC, is greater than 90%.

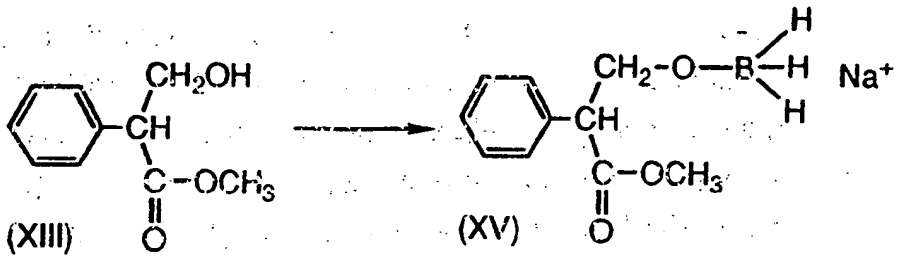
Tert-butyl methyl ether (200 mL) is charged to the reaction slurry, the resultant solution is transferred to a 2 liter separatory funnel. The layers are separated, the aqueous layer is washed with tert-butyl methyl ether (300 mL) and combined with the organic layer. Additional PPD can be recovered from the aqueous layer with multiple extractions of tert-butyl methyl ether. The combined organic layers are washed with 50% potassium carbonate solution (200 mL) and shaken until a precipitate of potassium carbonate forms. Water (60 mL) is added to dissolve most of the salts and the layers are separated. If needed, the pH of the aqueous layer is adjusted to 11 with 50% potassium carbonate solution. The organic layers are concentrated to an oil by rotovap distillation and residual tert-butyl methyl ether is chased by adding toluene (50 mL) and concentrating the solution on high vacuum rotovap distillation. The yield of the crude oil is 51 g, including residual toluene. Toluene (100 mL) is charged to the crude oil, heated to 65°C and the hot toluene solution containing PPD is filtered. The solution is cooled to room temperature, seeded with PPD, cooled and held at 0°C for 30 minutes and the resultant wet cake is washed with cold (0-5°C) toluene (50 mL) and dried at ambient temperature, then in a vacuum oven at 40-41°C with a nitrogen bleed to give 40 g of 2-phenylpropane-1,3-diol (PPD) as white crystals. A second recrystallization yields 38.2 g of PPD (63% yield).

Example 3. Preparation of 2-phenyl-1,3-propanediol (PPD) from methyl 2-formyl-2-phenylacetate sodium salt (VIII) via Route B.

An aqueous solution of methyl 2-formyl-2-phenylacetate sodium salt (VIII) from Preparative Example 2 is cooled to a temperature of -10°C to 0°C. Sodium borohydride (3.16 kg, 83.4 moles) is slowly added under a nitrogen atmosphere. Chilled isopropanol (56 liters) is charged at -10°C to 0°C. The reaction mixture is cooled at -15°C to -10°C. Glacial acetic acid (4.24 liters, 74.1 moles) is charged very slowly over a period of three

hours. The methyl 2-formyl-2-phenylacetate sodium salt (VIII) is protonated to a mixture of E-alpha-hydroxymethylene-phenylacetic acid methyl ester (X), Z-alpha-hydroxymethylene-phenylacetic acid methyl ester (XII) and formylphenylacetic acid methyl ester (XIV). This mixture (X, XII and XIV) converts in-situ to methyl tropate borate (XV). The temperature is maintained at -15°C to -10°C. Nitrogen gas is used to blanket the exothermic reaction, which evolves hydrogen gas. The reaction mixture is gently agitated for one hour. The reaction mixture is warmed to about 9°C and agitated overnight. As determined by HPLC, the methyl tropate borate (XV) is further converted to the borate esters (XVI) of PPD by reaction with the borohydrides present in the reaction mixture. Water (16 liters) is charged to the reaction mixture containing a mixture of borate esters (XVI) and the pH is adjusted between about 4.8 and 5.2 with concentrated hydrochloric acid to give a mixture of boric acid esters (XVII) and PPD (XVIII), as determined by proton nuclear magnetic resonance (NMR) spectral analysis. The reaction mixture is azeotropically distilled to remove the isopropanol and water, and the concentrated mixture is cooled to 20°C. The concentrated mixture containing 2-phenyl-1,3-propanediol or PPD (XVIII) and boric acid esters (XVII) is extracted with three, 32 liter portions of methyl tert-butyl ether. The combined methyl tert-butyl ether extracts are washed with two, 32 liter portions of aqueous potassium carbonate (40%) to further convert the boric acid esters (XVII) to PPD (XVIII). The organic layer is again washed with aqueous potassium carbonate. The combined aqueous potassium carbonate washes are back extracted with methyl tert-butyl ether. The combined organic layer containing PPD (XVIII), is concentrated to a volume of about 8 liters to which toluene (56 liters) is added. The mixture is distilled to remove residual tert-butyl ether and water. The concentrated mixture is filtered at 60°C, then cooled at 5°C. The precipitated PPD is filtered, washed with chilled toluene and dried in a vacuum oven with a nitrogen bleed at 30°C to give 6.4 kilograms (76% yield, +99% purity) of 2-phenyl-1,3-propane diol (PPD-XVIII). Recovery of PPD from the mother liquors increases the yield.

Example 4. Preparation of tropate borate (XV) from tropate (XIII)



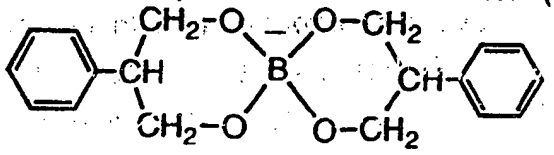
To a 3-neck reaction flask is charged methyl tropate (XIII, R=CH_3) (1.8 g, 0.01 mole) and methylene chloride (18 mL). The mixture is cooled to 0° to 5°C. Sodium borohydride (0.38 g, 0.01 mole) is charged in several portions at 0° to 5°C. Nitrogen gas is used to blanket the exothermic reaction, which evolves hydrogen gas. The reaction mixture is stirred at 0° to 5°C for 15 minutes. The reaction mixture is concentrated with rotovap at 18°C to produce 1.08 g (96% yield) of the title tropate borate (XV), a solid.

Example 5. Preparation of PPD from tropate (XIII) via Route C

To a 3-neck reaction flask is charged methyl tropate (XIII, 10.0 g, 0.056 mole) and isopropanol (60 mL). The mixture is cooled to -5°C to 0°C and sodium borohydride (3.2 g, 0.083 mole) is slowly charged to the flask producing methyl tropate borate (XV, R=CH_3). Then acetic acid (2.7 mL, 0.047 mole) is slowly charged to the reaction mixture to produce a mixture of borate esters (XVI). The reaction temperature is maintained at -5° to 0°C. Nitrogen gas is used to blanket the exothermic reaction, which evolves hydrogen gas. After 2.5 hours, isopropanol (20 mL) is charged to the thick reaction mixture at 5° to 10°C. Water (50 mL) is charged to the reaction mixture containing a mixture of borate esters (XVI). The pH is adjusted to 7.2 with 6N sulfuric acid (5.5 mL) to give a mixture of boric acid ester (XVII) and PPD (XVIII). The reaction mixture is azeotropically distilled to remove isopropanol and water. The concentrated mixture is cooled to 45°C and extracted with n-butanol (30 mL) at 40° to 45°C. After phases separation, the aqueous layer is extracted again with n-butanol (20 mL). The combined butanol extracts are charged with water (20 mL) and the pH is adjusted to ~2.0 with concentrated sulfuric acid. After phases separation, the organic layer is washed with water (10 mL). The organic layer is concentrated to a mixture of boric acid esters (XVII) of PPD and free PPD (XVIII). Methanol (40 mL) is charged to the thick oil, the methanol is distilled and the procedure is repeated. The boric acid ester of PPD (XVII, Y=OH) is cleaved to free PPD (XVIII) by azeotropic removal of methanol and trimethyl borate-methanol. Toluene (60 mL) is added

and the mixture is distilled to a final volume of 30 mL to remove residual methanol and water. The concentrated mixture is filtered at 60°C, cooled at 10° to 15°C to crystallize the PPD (XVIII). The reaction mixture is filtered, washed with toluene and dried in a vacuum oven with a nitrogen bleed at 20°C to give 6.1 g (73% yield, + 99% purity) of PPD (XVIII). Recovery of PPD from the mother liquors increases the yield.

Example 6. Preparation of borate diester (XVI) from PPD (XVIII)

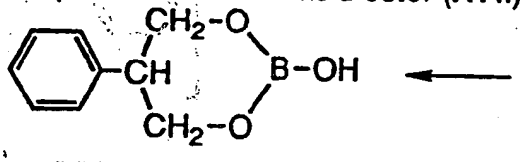


PPD (XVIII)

(XVI)

To a 3-neck reaction flask is charged 2-phenyl-1,3-propanediol (15.21 g, 0.1 mole), boric acid (3.09 g, 0.05 mole), sodium hydroxide (2.0 g, 0.05 mole) and toluene (243.4 mL). The reaction mixture is refluxed via Dean-Stark trap to remove water. The equilibrium is shifted towards borate diester (XVI) by removing water from the basic reaction mixture. After cooling to room temperature, the reaction mixture is filtered, washed with toluene and dried in a vacuum oven at 70°C to give 14.16 g (80% yield) of the title borate diester (XVI).

Example 7. Preparation of boric acid ester (XVII) from PPD (XVIII)

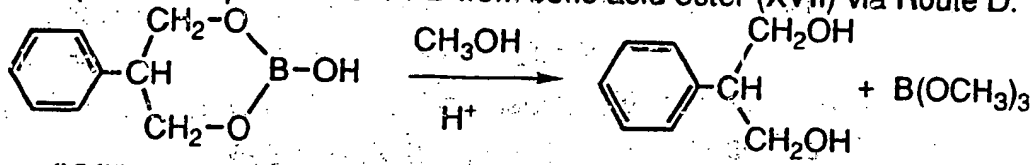


PPD (XVIII)

(XVII)

To a 3-neck reaction flask is charged 2-phenyl-1,3-propanediol (30.44 g, 0.2 mole), boric acid (12.37 g, 0.2 mole) and 243.4 mL of toluene. The reaction mixture is refluxed via Dean-Stark trap to remove water. The equilibrium is shifted towards boric acid ester (XVII) by removing water from the reaction mixture. After cooling to room temperature, the toluene is distilled and the reaction mixture is heated under vacuum to remove residual toluene. Cooling the resultant thick oil to room temperature gives 33.06 g (93% yield) of the title boric acid ester (XVII), a waxy solid.

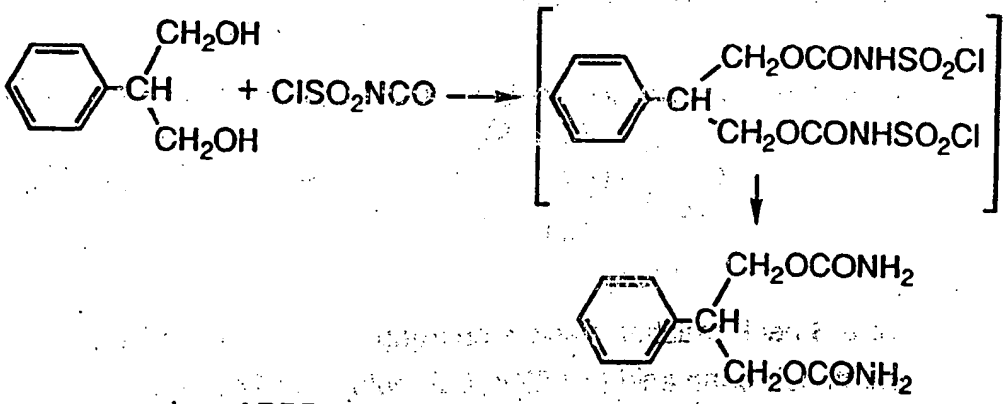
Example 8. Preparation of PPD from boric acid ester (XVII) via Route D.



(XVII) PPD (XVIII)

To a 3-neck reaction flask is charged boric acid ester (XVII, 17.8 g, 0.10 mole), methanol (53.4 mL) and sulfuric acid (0.1 mL). The mixture is heated to azeotropically distill methanol and trimethyl borate. During the distillation, boric acid ester (XVII) is slowly converted to PPD (XVIII). The distillation is repeated until boric acid ester is converted to >95% PPD, based upon analysis by ^{1}H-NMR. Toluene (89.0 mL) is added and the mixture is distilled to a final volume of about 70 mL to remove residual methanol. The concentrated mixture is cooled at 10-15°C to crystallize the PPD (XVIII). The mixture is filtered, washed with toluene and dried in a vacuum oven with a nitrogen bleed at 30°C to give 14.99 g (98% yield) of PPD (XVIII).

Example 9. Preparation of felbamate from PPD and chlorosulfonyl isocyanate



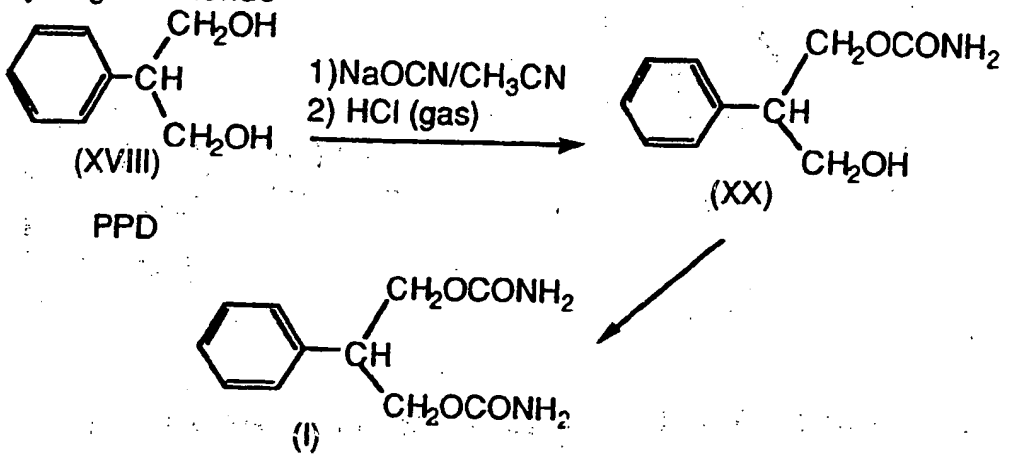
To a suspension of PPD (3.04 g, 0.02 mole) in 21 mL of toluene is added dropwise, at 10°C to 25°C, a solution of chlorosulfonyl isocyanate (CSI) (5.78 g, 0.04 moles) in 9 mL of toluene. The mixture is stirred at ambient temperature for two hours. Water (25 mL) is added dropwise while maintaining the temperature less than 50°C. The reaction mixture is stirred for 30 minutes, heated to 50°C for 20 minutes, cooled to ambient temperature and filtered to give 4.6 g of crude precipitated felbamate (96% yield).

Example 10. Preparation of PPD from Methyl phenylacetate via Route A

Sodium methoxide (24 g, 0.422 moles) is added to 160 mL of toluene under a nitrogen atmosphere, followed by addition of methyl phenylacetate (40 mL, 0.278 moles). The mixture is warmed to 40-45°C and methyl formate (27 mL, 0.427 moles) added while maintaining the reaction at 40 to 50°C. Following addition of methyl formate, the reaction mixture is agitated at 40-50°C for 30 minutes. A second charge of sodium methoxide (4 g, 0.070 moles) is added to the reaction mixture and the mixture is agitated at 40-50°C for 30 minutes. At the end of 30 minutes, analysis of the reaction mixture by HPLC indicates a conversion of methyl phenyl acetate to methyl 2-formyl-2-phenyl acetate sodium salt (greater than 95%, based upon disappearance of methyl phenylacetate starting material), leaving <3% of unreacted methyl phenylacetate. The reaction mixture is cooled to -5 to 0°C and slowly added to a precooled (-5-0°C) mixture of 160 mL water and 40 mL of n-butanol. The reaction vessel is rinsed with 40 mL toluene and added to the quenched mixture. The reaction mixture is maintained at -5 to 2°C. The aqueous phase containing methyl 2-formyl-2-phenylacetate sodium salt is rapidly added to a precooled (-5 to 0°C) mixture of 120 mL of n-butanol and 32 mL (0.559 mole) of glacial acetic acid. The organic phase containing the protonated enolate is slowly added to a mixture of 200 mL n-butanol and $NaBH_4$ (16 g, 0.422 moles) at -5 to 0°C, while maintaining the temperature of the exothermic reaction at -5 to 5°C. At the end of the addition, the reaction mixture is monitored by HPLC for completion. The reaction mixture is warmed to 10 to 15°C. At the end of 2 hours at 10 to 15°C, 20 mL of methanol is added to the reaction mixture. The reaction mixture is then maintained at 10 to 15°C until monitoring of the reaction mixture by HPLC indicates a conversion of methyl tropate to 2-phenyl-1,3-propanediol (PPD), leaving <3% unreacted methyl tropate. The reaction mixture is slowly warmed to 25°C, 320 mL water is slowly added, the temperature is maintained at 25°C and agitated for 5 minutes. The pH is adjusted to about 7.2 with concentrated sulfuric acid (~6.5 mL) and the temperature of the mixture is raised to 40°C. After phase separation, the aqueous layer is extracted again with 80 mL n-butanol (solution yield of PPD is ~90%). The combined butanol extracts are charged with 80 mL water and the pH is adjusted to about 2.2 with concentrated sulfuric acid (~1 mL) to give a mixture of boric acid esters and PPD. After phase

separation, the organic layer is washed with 40 mL water. The n-butanol layer is concentrated to give an oil containing a mixture of boric acid esters and PPD. Methanol (160 mL) is charged to the oil, concentrated, and distillation of 160 mL methanol is repeated. Toluene (200 mL) is added and the reaction mixture is azeotropically distilled, under vacuum, to a volume of 160 mL. The concentrated mixture is filtered at about 60°C then agitated to 25°C for about 30 minutes. The precipitated PPD is further chilled, filtered, washed at 0 to 5°C with toluene and dried in a vacuum oven with a nitrogen bleed at 25°C to give 32.0 grams (81% yield of recovered product, +99.3% purity) of 2-phenyl-1,3-propanediol. Recovery of PPD from the mother liquors increases the yield.

Example 11. Preparation of felbamate from PPD, sodium cyanate and hydrogen chloride

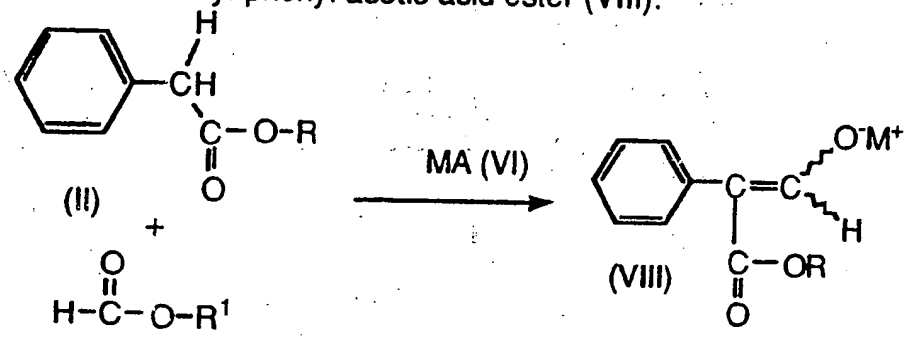


To a 4 L three-neck round bottom flask equipped with a thermometer and mechanical stirrer are charged 2-phenyl-1,3-propanediol (PPD) (152.19 g, 1.0 mole) and 760 mL of dry acetonitrile. The mixture is stirred at room temperature (20°C). Sodium cyanate (149.15 g, 2.29 mole) is charged and the mixture is cooled to -5°C. Hydrogen chloride gas is bubbled into the mixture at a rate of 1300 cubic centimeters (cc)/minute for 30 minutes until about 95 g (2.6 moles) of HCl is delivered into the mixture. The highly exothermic reaction is maintained below 35°C. Analysis of the reaction mixture by high performance liquid chromatography (HPLC) indicates a yield or conversion greater than (>) 95% of 2-phenyl-1,3-propanediol (XVIII) to felbamate (I), leaving less than 2% of monocarbamate alcohol (XX). The reaction is quenched by adding the mixture to 1.5 L of water and the resultant solution is neutralized to pH betwen 4 and 6 using 10% sodium hydroxide. The mixture is heated to 80°C until a clear solution forms. The hot solution is filtered and cooled to 10°C. The resultant heterogeneous solution is filtered. The filter cake is charged to 3.4 L of water, the pH of the mixture is adjusted to 2-2.5 with 2 N hydrochloric acid and the mixture is gently refluxed at 100°C for 5 hours. After cooling, the resultant heterogeneous solution is filtered. The wet cake is washed with two washings of 0.5 liter water and dried under vacuum with a nitrogen bleed at 100°C to give 214 g (90% overall yield) of purified felbamate (>99% purity).

Preparation of Starting Materials

In the illustration below, the enolate salt of formyl phenyl acetic acid ester (VIII) can be prepared by contacting a phenyl acetic acid ester (II)

with a formic acid ester (IV) in the presence of base MX (VI) to give the enolate salt of formyl phenyl acetic acid ester (VIII):



wherein R is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, aralkyl, substituted aralkyl, heterocyclic, heterocyclic alkyl, aryl or substituted aryl;

R^1 can represent the same values as R or another group capable of forming a leaving group R^1O^-, e.g., trimethylsilyl;

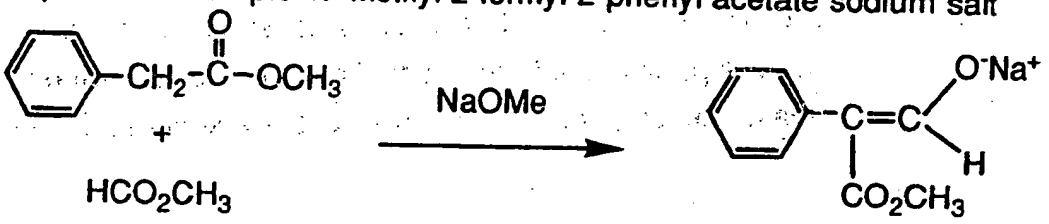
M is a cation, such as a metal of Groups I, II or III in the periodic table, titanium or ammonium; and

A is an anion which enables MX to function as a base, i.e., a hydride, alkoxide, amide or like moiety. Preferably R and R^1 are methyl and MX is sodium methoxide.

Esterification of phenyl acetic acid or formic acid with polyhydric alcohols, such as glycols, glycerols and pentaerythritols, gives bis, tris and tetra esters of phenyl acetic acid (II) and formic acid (IV). Such esters are useful for preparing the corresponding enolate salts.

The process can be carried out under conditions effective to yield the enolate salt of formylphenylacetic acid ester (VIII), such as described in Chemical Abstract 75(a): 63435q. The process for preparing the enolate salt (VIII) can be carried out neat or in the presence of any suitable organic solvent. Such solvents include aprotic solvents inert to the base used such as hydrocarbons, such as toluene, benzene and xylenes, or ethers such as diethylether, methyl tertiary butyl ether and the like. Where a base is employed, however, it is not essential that the base is soluble in the organic solvent. Suitable bases include hydroxides of the alkali and alkaline earth metals such as sodium hydroxide, potassium hydroxide and calcium hydroxide; hydrides such as sodium or potassium hydride; sodium methoxide; and potassium t-butoxide.

Preparative Example 1. Methyl 2-formyl-2-phenyl acetate sodium salt



Sodium methoxide (32.4 g, 0.6 mole) is added to 300 mL toluene. Small amounts of methanol and water are removed by azeotropic distillation. The mixture is cooled to 40-45°C and contacted with methyl phenyl acetate (45.1 g, 0.3 mole). The mixture is stirred for about 10 minutes at 45-50°C and methyl formate (19.8 g, 0.33 moles) is added. The temperature of the exothermic reaction is maintained at a temperature less than or equal to 50°C by the rate of addition of methyl formate. As the reaction progresses a heavy precipitate forms. At the end of 2.5 hours, analysis of the reaction mixture by high performance liquid chromatography (HPLC) indicates a conversion of methyl phenyl acetate to methyl 2-formyl-2-phenyl acetate sodium salt (94-95% yield, based upon the disappearance of the methyl phenyl acetate starting material), leaving 5-6% of unreacted methyl phenyl acetate. The solid is filtered and washed with two 50 mL washings with dry toluene to give a cake. The wet cake can be used in the next step or can be vacuum dried at a temperature less than or equal to 50°C and stored in a closed container.

Preparative Example 2. Aqueous solution of methyl 2-formyl-2-phenyl acetate, sodium salt

Sodium methoxide (VI) (4.74 kg, 83.4 moles) is added to 32 liters of methyl tert-butyl ether in a 50 gallon reactor under nitrogen atmosphere, followed by addition of methyl phenylacetate (II) (8 liters, 55.6 moles). The mixture is cooled to 10°C and methyl formate (IV) (4.5 liters, 72.3 moles) is slowly added, while maintaining the temperature of the exothermic reaction at 10°C to 20°C. Following addition of the methyl formate (IV), the reaction mixture is agitated at 25°C for up to three hours. At the end of 3 hours, analysis of the reaction mixture by high performance liquid chromatography (HPLC) indicates a conversion of methyl phenyl acetate to methyl 2-formyl-2-phenyl acetate sodium salt (VIII) (greater than 95% yield, based upon the disappearance of the methyl phenyl acetate (II) starting material), leaving 3% of unreacted methyl phenyl acetate. The reaction mixture is cooled to -5°C, chilled

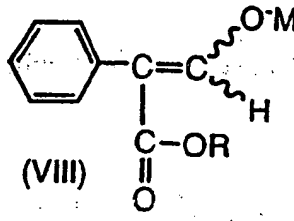
water (24 liters) is slowly added, the temperature is then maintained at 0°C and agitated for 10 minutes. After standing for 15 minutes, the mixture partitions into an organic and an aqueous phase. The aqueous phase contains methyl 2-formyl-2-phenylacetate sodium salt (VIII).

CLAIMS:

1. A process for preparing 2-phenyl-1,3-propanediol (PPD-XVIII), comprising:

reacting a compound which is:

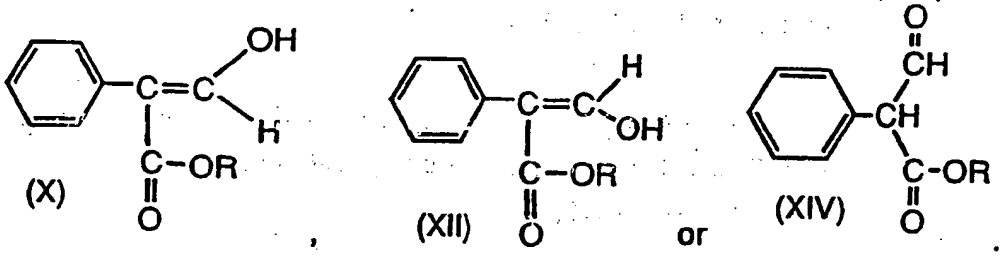
i) the enolate salt of formyl phenyl acetic acid ester (VIII)



(VIII)

;

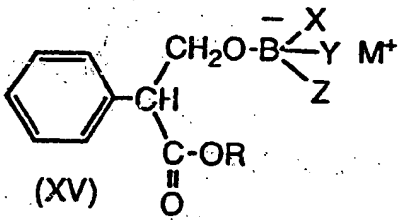
ii) an E-enol (X), a Z-enol (XII) or formylphenylacetic acid ester (XIV)



(X) , (XII) or (XIV)

;

iv) a tropate borate (XV)



(XV)

; or

or a mixture thereof, wherein

M is a cation;

R is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, arylalkyl, substituted arylalkyl, heterocyclic, heterocyclic alkyl, aryl or substituted aryl;

X, Y and Z independently represent H, -OH, $-O^-M^+$, $-O-R^2$ or $-OCOR^2$ where M is as defined hereinabove, and R^2 is C-1 to C-6 alkyl;

with an acid and a borohydride reducing agent in an amount effective to give PPD.

2. The process of claim 1 wherein the enolate salt (VIII) is methyl 2-formyl-2-phenyl acetate sodium salt.

3. The process of claim 1 wherein the reactant compound is ii)

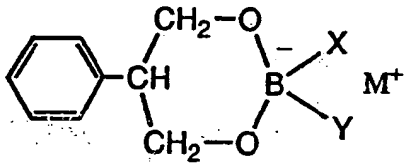
E-enol (X), Z-enol (XII) or formyl phenyl acetic acid ester (XIV) or a mixture thereof.

4. The process of claim 1 wherein the reactant compound is formyl phenyl acetic acid ester (XIV).

5. The process of claim 1 wherein the reactant compound is iv) tropate borate (XV).

6. The process of claim 1 wherein the acid is sulfuric acid or acetic acid and the borohydride reducing agent is sodium borohydride or potassium borohydride.

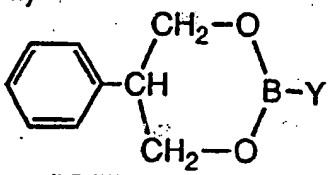
7. A process for preparing 2-phenyl-1,3-propanediol (PPD-XVIII), comprising cleaving a compound which is:
v) a borate ester (XVI)



(XVI)

;

vi) a boric acid ester (XVII)



(XVII)

; or

or a mixture thereof; wherein
M is a cation;
X and Y independently represent H, -OH, -O$^-$M$^+$, -O-R^2 or -OCOR^2 where M is as defined hereinabove, R^2 is C-1 to C-6 alkyl, to give PPD.

8. The process of claim 7 where the borate ester (XVI) or boric acid ester (XVII) is cleaved in the presence of an acid.

9. The process of claims 7-8 wherein borate ester (XVI), boric acid ester (XVII) or mixtures thereof is cleaved by extraction and/or by distillation.

10. The process of claim 7-9 wherein borate ester (XVI), boric acid ester (XVII) or mixtures thereof is cleaved by extracting with water and a suitable organic solvent.

11. The process of claim 7-9 wherein borate ester (XVI), boric acid ester (XVII) or mixtures thereof is cleaved by hydrolysis and transesterification of the reaction mixture, followed by distilling out the volatile borates formed therefrom.

12. The process of claims 1-11 wherein the 2-phenyl-1,3-propanediol (PPD-XVIII) thus prepared is converted to 2-phenyl-1,3-propanediol dicarbamate (felbamate-I).

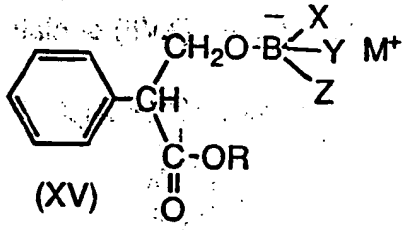
13. The process of claims 1-2 wherein the enolate salt of formyl phenyl acetic acid ester (VIII) is prepared by contacting an ester of phenyl acetic acid (II) with an ester of formic acid (IV) in the presence of a base of the formula:

MA (VI)

wherein M is a cation and wherein A is an anion which enables MA to function as a base, to give the enolate salt of formyl phenyl acetic acid ester (VIII).

14. The process of claim 13 wherein the ester of phenyl acetic acid (II) is methyl phenyl acetate, the base is sodium methoxide and the ester of formic acid (IV) is methyl formate.

15. A tropate borate (XV) of the formula:



(XV)

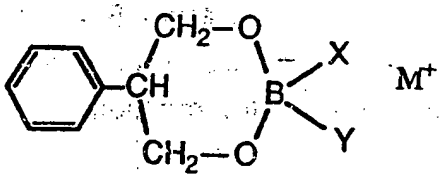
wherein X and Y independently represent H, -OH, $-O^-M^+$, $-O-R^2$ or $-OCOR^2$,

M is a cation;

R^2 is C-1 to C-6 alkyl; and

R is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, arylalkyl, substituted arylalkyl, heterocyclic, heterocyclic alkyl, aryl or substituted aryl.

16. A borate ester (XVI) of the formula:



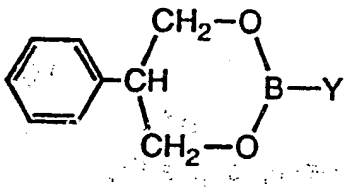
(XVI)

wherein X and Y independently represent H, -OH, $-O^-M^+$, $-O-R^2$ or $-OCOR^2$ where

M is a cation; and

R^2 is C-1 to C-6 alkyl.

17. A boric acid ester (XVII) of the formula:

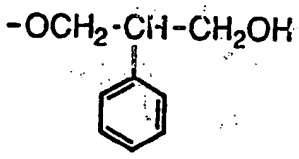


(XVII)

wherein Y is -OH, -OM, $O-R^2$ or $-OCOR^2$ wherein M is a metal of Groups I, II or III of the periodic table and R^2 is C-1 to C-6 alkyl.

18. The boric acid ester (XVII) of claim 18 wherein Y is -OH.

19. The boric acid ester (XVII) of claim 18 wherein Y is $-OR^2$ and R^2 is



C-1 to C-6 alkyl or

20. The boric acid ester (XVII) wherein Y is $-OCOR^2$.

21. A process for preparing felbamate, comprising contacting 2-phenyl-1,3-propanediol with either

a) a cyanate and a strong acid in a non-halogenated solvent which can provide felbamate in a yield of about 70% or greater; or
b) chlorosulfonyl isocyanate in a suitable solvent.

22. The process of claim 21 wherein the solvent is ethylene glycol dimethyl ether, acetonitrile, N,N-dimethyl acetamide or mixtures thereof.

23. A process for preparing felbamate which comprises converting the hydroxy groups of PPD to $-OCONH_2$ characterized in that the PPD used as a starting material is produced using a procedure of any of claims 1-11.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C29/147 C07C33/26 C07C269/00 C07C269/02 C07F5/02 C07F5/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF ORGANIC CHEMISTRY vol. 54 , 1989 , EASTON US pages 1194 - 1198 Y CHOI ET AL 'EFFECT OF TEMPERATURE ON BORANE REDUCTION OF REPRESENTATIVE MALONIC ACIDS' see the whole document ---	1
X	JOURNAL OF ORGANIC CHEMISTRY vol. 54 , 1989 , EASTON US pages 1198 - 1200 Y CHOI ET AL 'A SIMPLE CONVERSION OF DIETHYL PHENYLMALONATE WITH METAL HYDRIDE TO THE CORRESPONDING PRIMARY DIOL: A COMPETING REACTION BETWEEN REDUCTION AND METALATION' see the whole document ---	1
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 1994	03. 02. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Heywood, C

International Application No
PCT/US 93/08450

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 93-280746 & US,A,5 239 121 (GANES CHEM INC) 24 August 1993 see abstract	1
A	US,A,5 091 595 (Y CHOI) 25 February 1992 cited in the application see the whole document	1
X	see examples 3,4	23
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 76-93721X & SU,A,322 988 (ORDZHONIKIDZE CHEM-PHARM) 31 March 1976 cited in the application see abstract	1
A	DATABASE WPI Derwent Publications Ltd., London, GB; AN 74-52707V & JP,A,49 036 653 (NIPPON SHINYAKU) 5 April 1979 see abstract	21
A	L FIESER ET AL 'REAGENTS FOR ORGANIC SYNTHESIS' 1967 , WILEY , NEW YORK,US see page 117	21